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# Maine Agricultural Experiment Station.

ORONO

BULLETIN No. 201.

JUNE, 1912.

SPIRIT OF NITROUS ETHER.

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## BULLETIN 201.

### THE DETERIORATION AND ASSAY OF SPIRIT OF NITROUS ETHER.

H. H. HANSON AND A. K. BURKE.

Spirit of Nitrous Ether, commonly called Sweet Spirit of Nitre, an alcoholic solution of ethyl nitrite, has been for a century and a half, or more, a preparation of importance in medicine. Strictly speaking, the preparation as it is now made is somewhat different from the original Sweet Spirit of Nitre. Different methods have been used in its preparation and different names have been applied to the product. At the present time it may be made in this country according to the method given in the eighth revision of the United States Pharmacopoeia (1900), or it may be prepared by diluting concentrated nitrous ether which may be purchased for the purpose in small sealed tubes or bottles.

#### DETERIORATION.

From the first it has been recognized as a very unstable compound, liable to deterioration and decomposition unless kept under the most favorable conditions. Upon standing, the ethyl nitrite (upon which this preparation is supposed to depend for its efficiency) gradually decreases in amount and, at the same time, undesirable compounds are, and even dangerous compounds may be, formed. The following list of possible decomposition products is taken from a well known authority;\* Aldehyde, paraldehyde, ethyl acetate, ethyl nitrate, nitrous acid, acetic acid, ethyl oxide, ethyl formate, ethyl oxalate, cyanogen compounds, glyoxal, glyoxalic acid, oxalic acid, malic acid, saccharic acid, and nitro ethane. In order to reduce the liability of decomposition to the lowest degree the United States Pharmacopoeia directs that the preparation be kept in "small, well-stoppered, dark, amber-colored vials, in a cool place, remote from lights or fire." In order to test the value of these directions three lots were prepared from tubes of concentrated

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\* Allen's Commercial Organic Analysis Vol. I, p. 194.

nitrous ether according to directions. These samples were carefully tested and then stored as follows: Sample A was kept in a dark amber-colored bottle, full to the top, in the dark, in a refrigerator, strictly according to Pharmacopoeia directions. Sample B was kept in an amber-colored bottle tightly corked with a cork stopper, at ordinary room temperature in a dark cupboard. The bottle was full at the beginning of the experiment. Sample C was kept in a green colored bottle in the same cupboard with B but the bottle was only half full at the beginning. These three experiments were not made at exactly the same time and the intervals between the different assays were not the same in the three different cases. From table 25 it will readily be seen, however, that sample A, kept strictly according to directions, remained for two months at exactly the same strength found by the first test and that during the next month it lost only 0.23 per cent of ethyl nitrite. This sample when made up carried 4.06 per cent, and at the end of 90 days 3.83 per cent of ethyl nitrite. In order that the conditions under which sample A was kept approximate as near as possible the conditions existing in a drug store, each time the sample was opened and assayed two or three ounces were turned out in imitation of a sale.

Sample B was kept in an amber-colored bottle under the same conditions which surrounded A with the exception that it was kept at ordinary room temperature. Results of the assay of this sample show that the decrease in strength began at once and that the decrease was steady but not rapid. The sample at the beginning contained 4.21 per cent ethyl nitrite. In seventy days the strength had dropped to 3.93 per cent, and in one hundred and sixty-six days to 3.80 per cent ethyl nitrite.

Sample C, kept in a green bottle only half full, at room temperature, in the same closet with sample B, decreased in strength from 3.86 per cent at the beginning to 3.48 per cent of ethyl nitrite at the end of 170 days.

The results are given in Table 25. Sample A was stored as the preparation should always be kept and the result indicates that under these favorable conditions sweet spirit of nitre will keep for several months practically uniform. Samples B and C were stored as such material is often kept in drug

stores and the result shows that under such circumstances decomposition begins at once and steadily continues.

It was not considered necessary to try samples kept under extremely unfavorable conditions as it is well known that exposure to light, high temperature, and free access of air contribute to rapid deterioration.

TABLE 25.

*Deterioration of Samples of Sweet Spirit of Nitre Stored under Different Conditions.*

SAMPLE A.				
DATE OF TEST.	Elapsed Time—Days.	Corrected Reading—C. C.	Ethyl nitrite. Per Cent.	Deterioration. Per Cent.
June 3.....	—	55.9	4.06	—
June 16.....	13	55.9	4.06	0.00
July 17.....	44	55.8	4.06	0.00
August 3.....	61	55.8	4.06	0.00
August 18.....	76	54.6	3.97	0.09
September 1.....	90	52.7	3.83	0.23

SAMPLE B.				
March 19.....	—	—	4.21	—
March 27.....	8	54.9	3.99	0.22
April 30.....	42	54.7	3.98	0.23
May 28.....	70	54.1	3.93	0.28
September 1.....	166	52.3	3.80	0.41

SAMPLE C.				
March 16.....	—	—	3.86	—
March 27.....	11	49.9	3.63	0.23
April 30.....	45	49.4	3.59	0.27
August 4.....	141	48.3	3.51	0.35
August 18.....	155	48.0	3.49	0.37
September 2.....	170	47.9	3.48	0.38

In Table 25 the first readings under samples B and C, 4.21 per cent and 3.86 per cent, may possibly be slightly high because these two samples, made from tubes of concentrated nitrous ether, were among the first investigated and it was

shortly afterwards found that an analysis made immediately following the preparation of the sample might not give correct results unless unusual care had been observed in the mixing. This is a point of importance to the pharmacist as it indicates that the concentrated nitrous ether mixes but slowly with alcohol unless it is very thoroughly shaken.

### METHODS OF ANALYSIS.

Three different methods of assaying spirit of nitrous ether have been proposed: that given in the seventh revision of the United States Pharmacopoeia, that given in the eighth revision of the same publication, and a modification or combination of the two which may be found outlined in Schimpf's *Manual of Volumetric Analysis*.<sup>\*</sup> These methods as given are as follows:

*Method of Assay According to Seventh Revision of the U. S. P. 1890.* "If 5 Cc. of recently prepared Spirit of Nitrous Ether be introduced into a nitrometer, and followed, first, by 10 Cc. of potassium iodide T. S., and then by 10 Cc. of normal sulphuric acid, the volume of nitrogen dioxide generated at the ordinary indoor temperature (assumed to be at or near 25° C., or 77° F.) should not be less than 55 Cc. (corresponding to about 4 per cent of pure ethyl nitrite)."

*Method of Assay According to the Eighth Revision of the U. S. P. 1900.* "Transfer about 30 Gm. of the Spirit of Nitrous Ether, which has been previously shaken with 0.5 Gm. of potassium bicarbonate, to a tared 100 Cc. measuring flask, and weigh it accurately. Add sufficient alcohol to bring the volume to exactly 100 Cc., and mix thoroughly. Introduce into a nitrometer (see Appendix, Gasometric Estimations) exactly 10 Cc. of the alcoholic solution, followed by 10 Cc. of potassium iodide T. S., and afterwards by 10 Cc. of normal sulphuric acid V. S. When the volume of gas has become constant (within 30 to 60 minutes), note the volume of gas collected. Multiply this volume in Cc. by 0.307, and divide the product by the original weight of the Spirit of Nitrous Ether. At standard temperature and pressure the quotient will represent the percentage of

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<sup>\*</sup> Fifth Edition, p. 683.



ethyl nitrite in the liquid. The temperature correction is one-third of one per cent of the total percentage just found for each degree, additive if temperature is below, subtractive if above,  $25^{\circ}$  C. ( $77^{\circ}$  F.). The barometric correction is four-thirtieths of one per cent for each millimeter, additive if above, subtractive if below, 760.

When assayed according to the above method, Spirit of Nitrous Ether should yield not less than 4 per cent of ethyl nitrite."

*Schimp Method.* This determination, which is to be conducted with a nitrometer, is outlined thus: "Open the stop-cock of the measuring tube, raise the control-tube, and pour into the latter a saturated solution of NaCl until the measuring tube, including the bore of the stop-cock, is completely filled. Then close the stop-cock and fix the control-tube at a lower level. Now introduce into the funnel at the top of the measuring tube a weighed quantity (about 4 gms.)\* of spirit of nitrous ether; open the stop-cock, and allow the spirit to run into the nitrometer, being careful that no air enters at the same time. 10 Cc. of potassium iodid T. S. are now added in the same manner, and followed by 10 Cc. of normal sulphuric acid V. S. Effervescence takes place immediately, and after 30 to 60 minutes, when the volume of gas becomes constant, the control-tube is lowered so as to make the level of the liquid in both tubes the same, and the volume of the gas in the graduated tube read off.

This volume, multiplied by 0.0030673 gm. gives the weight of ethyl nitrite in the spirit taken for analysis. The product multiplied by 100, and then divided by the weight of the spirit taken, gives the per cent of pure ethyl nitrite present."

Barometric and temperature corrections are to be made as usual.

A method similar to the latter was tried several years ago by one of the authors upon the theory that it was more accurate than the old and certainly easier of manipulation than the new U. S. P. method.

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\* It is convenient to take 5 Cc. accurately measured, and calculate its weight by multiplying by the specific gravity.

In order to compare the accuracy of these three methods a large number of assays were made on samples of various ages and strengths and the results are given in Table 26.

TABLE 26.

*Analysis of Sweet Spirit of Nitre by Three Methods.*

STATION NUMBER.	Ethyl nitrite by U. S. P. method, 1890.	Ethyl nitrite by U. S. P. method, 1900.	MODIFIED METHOD.				
			Ethyl nitrite calculated from weight.	Ethyl nitrite calculated from Sp. Gr.	Specific gravity, 24° C.	Weight taken.	Weight cal- culated from Sp. Gr.
10,525	-	4.11	4.16	-	-	4.2080	-
10,527	3.48	-	3.56	3.59	0.8225	4.1280	4.1125
10,529	4.02	3.97	4.12	4.12	0.8183	4.0855	4.0915
10,531	4.34	-	4.46	4.47	0.8163	4.1055	4.0815
10,533	2.46	-	2.52	2.52	0.8224	4.1170	4.1120
10,538	3.06	-	3.16	3.16	0.8206	4.1060	4.1030
10,543	4.17	-	4.21	-	-	4.1895	-
10,544	2.60	2.61	2.67	2.69	0.8177	4.1240	4.0885
10,547	3.34	3.14	3.37	3.40	0.8288	4.1820	4.1440
10,549	4.40	4.25	4.52	4.56	0.8133	4.1000	4.0665
10,550	3.81	3.50	3.94	3.96	0.8133	4.0810	4.0665
10,552	3.52	3.50	3.63	3.62	0.8217	4.0925	4.1055
10,560 A	4.59	4.48	4.71	4.74	0.8160	4.1110	4.0800
10,560 B	4.50	4.56	4.62	4.64	0.8160	4.1040	4.0800
10,560 C	-	4.47	-	-	0.8160	-	-
10,561	3.89	3.58	4.01	4.03	0.8141	4.1185	4.0705
10,562	4.10	3.81	4.20	4.22	0.8201	4.1280	4.1005
10,563	3.10	3.01	3.19	3.21	0.8152	4.0935	4.0760
10,568 A	4.07	4.02	4.20	4.24	0.8118	4.1025	4.0590
10,568 B	4.07	3.75	4.19	4.23	0.8118	4.1040	4.0590
10,568 C	3.97	-	4.11	4.13	0.8118	4.0800	4.0590
10,568 D	4.07	-	4.22	4.23	0.8118	4.0730	4.0590



Referring to table 26 it will be seen that the result obtained by the new United States Pharmacopoeia method is in every case the lowest, and that the result obtained by the modified method is in each case the highest, when compared with the results by the other methods on the same sample. That this difference represents an actual gain in accuracy for the modified method seems apparent when the work and results are carefully analyzed.

The manner in which the determination is made by the modified method when absolute accuracy is desired is as follows: The nitrometer shown in the illustration, Fig. 268, is filled to the top of the stem of the thistle tube with a saturated salt solution, which is drawn down to the bottom of the ungraduated arm by means of the outlet tube at the bottom after the stop-cock at the top has been closed; thus leaving the graduated arm full but under reduced pressure. The bottle containing the sample is weighed and then five cubic centimeters are withdrawn in a pipette and the bottle again weighed. This five c. c. portion is placed in the thistle tube, drawn down, and washed in with a few drops of alcohol. Then in succession ten cubic centimeters of a ten per cent solution of potassium iodide and ten cubic centimeters of a five per cent solution of sulphuric acid are introduced in a like manner, taking care that no air is accidentally drawn in during the process. In order to obtain all of the five c. c. portion of the sweet spirit of nitre which was drawn from the bottle the potassium iodide solution is allowed to run through the pipette and wash out into the nitrometer every trace of the sample. Nitrogen dioxide gas,  $\text{NO}_2$ , is immediately formed, and, by means of the outlet tube at the bottom, the salt solution is drawn down so that the level of the liquid in the ungraduated branch is kept below that in the graduated. The reaction is rapid for the first two or three minutes and then proceeds slowly for an indefinite period. The process should be allowed to continue for one hour with frequent shaking and the volume of the gas is then read with the liquid in the two tubes at the same level. This volume multiplied by 0.0030673, the product multiplied by 100, and then divided by the weight of the sample taken, gives the per cent of ethyl nitrite present after the result is corrected for temperature and pressure.

When the assay is carefully made by this method every trace of the weighed sample is used and there is no chance for the escape of gas. That the result is more accurate than that obtained by the U. S. P. method of 1890 is evident from the fact that the sample is accurately weighed. Different samples vary in specific gravity as shown in Table 26 and, therefore, if volume alone is considered, as in the old U. S. P. method, the result can not be absolutely correct unless by accident. It is of interest to compare the percentage of ethyl nitrite found when the weight obtained by difference, as above, is used as a basis and when the weight is calculated from the specific gravity.

In the 19 results thus compared in Table 26 three are alike, the greatest difference is 0.04 per cent, and the average difference is only 0.02 per cent.

If the modified method is more accurate than the old U. S. P. method a study of Table 26 will show that it is more accurate than the new U. S. P. method, of 1900, as this gives the lowest average results of either of the three. Compared with the old U. S. P. method the modified method gives results ranging higher from 0.03 per cent to 0.25 per cent. Compared with the new U. S. P. the modified method gives results ranging higher from 0.05 per cent to 0.47 per cent. Comparing the old and new U. S. P. methods it is found that in twenty cases the old method gives the highest results, the differences running from 0.02 per cent to 0.32 per cent; while in three cases the new method gives the highest, running however only from 0.01 per cent to 0.06 per cent.

The modified method gives uniform results when tried several times upon the same sample, while among the results obtained by the new U. S. P. method will often be found variations similar to that noted in Table 26 under sample number 10508. A and B. Compared with the new U. S. P. method the modified method is less expensive in both time and chemicals. In eliminating the shaking out with potassium bicarbonate no error is introduced because if absolute accuracy is required any free acid present may be washed into the nitrometer with alcohol before it comes in contact with any reagent; while on the other hand the process is simplified thus reducing the chance for error or loss. That the use of potassium bicar-

bonate does not make any appreciable difference is shown in Table 27 which gives the results on the same samples, using the modified method, both with and without the reagent in question. It will be noted that in two cases slightly higher results were obtained when using the bicarbonate while in two other cases the reverse was true. These differences, however, are so small that they might occur when the determinations were made as nearly alike as it is possible to duplicate, and indicate no advantage obtained by the use of potassium bicarbonate. In these cases the shaking out was done directly in the sample bottle after the first determination had been made.

TABLE 27.

*Analysis of Sweet Spirit of Nitre With and Without the Use of Potassium Bicarbonate.*

NUMBER.	ETHYL NITRITE FOUND. PER CENT.	
	Modified Method.	Modified Method Using $\text{KHCO}_3$
10,495	3.48	3.40
10,510	2.68	2.70
10,563	2.96	3.03
10,579	4.46	4.44

The sentence quoted below from the Pharmacopoeia of 1900, and which appears also in the Schimpf Method, "when the volume of gas has become constant (within thirty to sixty minutes) note the volume of gas collected" would lead one unfamiliar with this reaction to suppose that the volume of gas did become constant within an hour. As a matter of fact it very seldom or never does. Experiments were made to determine, if possible, when the volume of gas did finally become constant and also to determine, if possible, a factor which might be applied to correct for the volume of gas generated after the one hour period. Determinations were allowed to run for various periods up to three days and at the end of this 72 hours the volume of gas was still increasing very slowly. In Table 28 the results of these observations are given. In the second column is given the corrected reading taken after the hour period had elapsed and upon which was

calculated the assay of that particular sample. That the reaction was not complete, however, is shown by the series of second readings taken after periods ranging from 16 to 72 hours after the first reading. The differences between the two readings, while ranging from 0.2 to 2.2 cubic centimeters do not correspond to the differences in time. For example, one sample after standing 24 hours had increased 0.8 cubic centimeter, while another sample after standing for the same period had increased 2.0 cubic centimeters. One sample standing 72 hours increased 2.2 cubic centimeters, while another for the same period increased only 1.3 cubic centimeters. This increase seemed never the same in any two cases and varied at different times during the periods themselves. The rate of increase depends on so many different factors, such as strength of the sample, its age, the amount of water present, compounds which may have been formed by decomposition, and not only the temperature and pressure at the time of beginning the experiment, but the variations while the test is being made, that it is impossible to apply any corrections and the best that can be done is to establish some uniform rule in regard to the time. One hour was finally adopted and if the apparatus is shaken several times during the interval so that the reagents are thoroughly mixed, the gas generated in sixty minutes is near enough to the total amount for all practical purposes.

TABLE 28.

*Variation in the Rate at Which Nitrogen Dioxide Gas is Liberated in the Analysis of Sweet Spirit of Nitre under Different Conditions.*

Number.	CORRECTED READINGS, c. c.		Time Elapsed— Hours.	Difference, c. c.	TEMPERATURE, DEGREES C.	
	First.	Second.			First Reading.	Second Reading.
1	55.9	56.1	16	0.2	21.0	20.0
2	55.5	56.4	17	0.9	23.5	22.0
3	56.8	57.8	22	1.0	20.3	21.0
4	53.9	54.7	24	0.8	21.0	22.0
5	48.3	50.3	24	2.0	22.2	20.5
6	55.4	56.7	48	1.3	—	20.0
7	49.9	51.2	72	1.3	—	22.3
8	44.2	46.4	72	2.2	21.5	21.5

## SUMMARY.

In conclusion emphasis should be given to four points which may be summarized as follows:

1. When Sweet Spirit of Nitre is made from concentrated nitrous ether the product should be shaken for several minutes to insure thorough uniformity.

2. A sample of Sweet Spirit of Nitre kept strictly in accord with Pharmacopoeia directions remained constant in strength for 60 days and deteriorated but slightly during the next 30 days. Under unfavorable conditions decomposition of samples began at once and steadily continued.

3. The Modified Method of analysis, as described in detail, gives more accurate results than either the old or the new Pharmacopoeia methods, and compared with the latter is more economical in time and reagents and is easier of manipulation, with less chance for error. For a quick method when extreme accuracy is not required the old U. S. P. method (1890) gives approximately correct results.

4. When determining the ethyl nitrite in sweet spirit of nitre by the liberation of nitrogen dioxide the volume of gas does not become constant in "from thirty to sixty minutes" as published directions would lead one to suppose, but increases slowly, and at a varying rate, which is influenced by numerous different conditions, sometimes at least, for several days. For this reason it is not practicable to attempt to obtain an absolutely constant volume, nor to apply a factor to correct for these last traces of gas, and a one hour period for the reaction to take place, with frequent shaking, may be used with practically correct results.



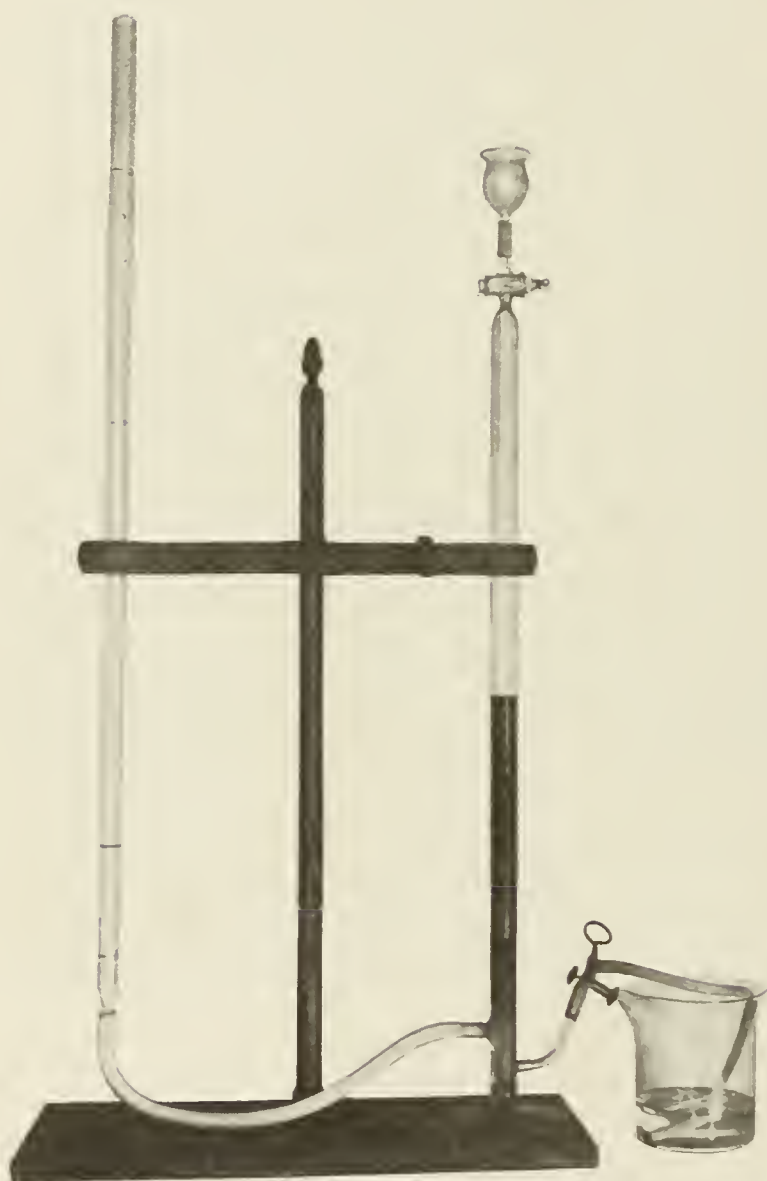


Fig. 268. Nitrometer used in assay of sweet spirit of nitre.



